

Treating chancroid: summary of studies in southern Africa

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SUMMARY Recent studies undertaken in southern Africa and elsewhere indicate that many short or single dose treatments are available to treat chancroid. Erythromycin 500 mg three times a day for five days, ciprofloxacin 500 mg, sulphamethopyrazine 800 mg and trimethoprim 1000 mg or sulphametrole 3200 mg and trimethoprim 640 mg as single oral doses, or ceftriaxone 250 mg as a single intramuscular injection are all effective in treating the disease. The widespread use of these regimens largely depends on the accuracy of diagnosis, susceptibilities of local *Haemophilus ducreyi* isolates to antimicrobials, and financial considerations.

Chancroid is endemic in many tropical countries of Africa¹⁻⁴ and South East Asia,⁵⁻⁷ and has been recorded increasingly in areas remote from the tropics.^{8,9} The disease, which is characterised by painful ulcerative lesions of the genitalia and is often associated with painful regional lymphadenopathy, may easily be misdiagnosed as primary syphilis, lymphogranuloma venereum (LGV), or genital herpes. Until recently sulphonamides and tetracyclines were accepted as the treatment of choice for the disease.¹⁰ Cases refractory to treatment with these antimicrobial agents have, however, been recorded in both the Far East and Africa.^{11,12}

The availability of a solid agar medium devised by Hammond *et al* in 1978,¹³ which was subsequently modified to yield an isolation rate of more than 80%,² heralded reliable testing of the susceptibility of *Haemophilus ducreyi* to antimicrobials. Initial testing of low passage isolates confirmed that they were resistant to sulphonamides (MIC₉₀ > 128 mg/l) and tetracycline (MIC₉₀ > 16 mg/l) and to penicillin because they produced β lactamase, but were susceptible to erythromycin and co-trimoxazole (sulphamethoxazole and trimethoprim).¹⁴ Multidose treatment with one of these two antimicrobial preparations has largely become the treatment of choice for chan-

croid. Recent studies have indicated that newer compounds, which show good in vitro activity against *H ducreyi* and have the required pharmacokinetic properties, may yield satisfactory cure rates (> 90%) if given as a single dose. We summarise the results of studies undertaken in southern Africa and elsewhere and discuss the implications for future treatment of the disease.

Patients

The patients were mine workers with clinical signs consistent with a diagnosis of chancroid who attended a clinic at the Leslie Williams Memorial Hospital, Carletonville, South Africa, or patients attending clinics for sexually transmitted diseases at the Hillbrow Hospital, Johannesburg, South Africa, or Mbare Clinic, Harare, Zimbabwe. A detailed history was taken from each patient and the number, size, site, and clinical features of genital lesions and the presence and extent of associated lymphadenopathy were noted. If more than one ulcer was present, the largest (the target ulcer) was selected for study.

Collecting specimens

The ulcers were cleaned thoroughly and collected from their bases, using a platinum scraper (Kimura spatula: Storz Instruments, St Louis, Missouri, USA), serous material that was examined by dark field microscopy for *Treponema pallidum*. Thereafter, material from the

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bases of target ulcers was collected on calcium alginate swabs (Calgiswab, Code No 60-150-28; Inolex, Glenwood, Illinois, USA) and used to try to isolate *H ducreyi*, herpes simplex virus (HSV), and *Chlamydia trachomatis*. Isolation of *H ducreyi* and *C trachomatis* was also attempted from aspirates obtained from fluctuant inguinal lymph nodes and from inguinal ulcers. Serological tests for syphilis (rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption (FTA-ABS) tests) and chlamydial infection (a modified microimmunofluorescence technique)¹⁵ were performed for each patient.

Laboratory methods

Ulcer material was inoculated on to two solid selective media, one comprising Mueller-Hinton agar base (BBL Division, Becton-Dickinson, Cockeysville, Maryland, USA) with 5% chocolate horse blood, 1% IsoVitaleX, and 3 mg/l vancomycin, and the other comprising gonococcal agar base (Gibco Laboratories, Madison, Wisconsin, USA) with 2% bovine haemoglobin, 5% fetal calf serum, 1% IsoVitaleX, and 3 mg/l vancomycin. All inoculated plates were placed in a candle extinction jar and kept at room temperature for up to six hours, after which they were transferred to a microaerophilic atmosphere (provided by an anaerobic jar from which the catalyst had been removed) and incubated at 35°C for 48–72 hours.

Typical colonies of *H ducreyi* that could be pushed intact across the agar surface were identified according to the criteria of Kilian.¹⁶ Swabs for isolating *C trachomatis* and HSV were inoculated into transport media and kept at 4°C for up to 24 hours. They were either processed within that period or frozen at –70°C. We attempted to isolate *C trachomatis* using cycloheximide treated McCoy cells,¹⁷ and HSV using human foreskin fibroblasts.

Patients were excluded from the studies if they failed to give informed consent or had received any antimicrobial chemotherapy within the previous seven days or if dark field examination of their ulcer exudate proved positive for syphilis. Patients were subsequently excluded if *C trachomatis* or HSV were recovered from their lesions or if *H ducreyi* was not isolated. Patients with positive or presumptive serological evidence of syphilis or LGV (chlamydial microimmunofluorescence titres $\geq 1/256$) were not excluded. Patients took single dose treatment under direct supervision. They were asked to refrain from sexual contact and to return for two follow up examinations (on days 7–10 and 14–21). Cultures for *H ducreyi* were repeated if the target ulcer had not re-epithelialised, if the lymph nodes had become fluctuant, or if an inguinal ulcer had formed or persisted.

Results

ERYTHROMYCIN

Erythromycin has emerged as one of the drugs of choice for treating chancroid on the basis of both in vitro and in vivo data.^{14,18} The dosage and duration of treatment with this antibiotic, however, have remained in question.¹⁸

During a dose finding (unpublished) study three regimens involving six patients receiving a single dose of 1500 mg erythromycin, five patients receiving 500 mg three times a day for three days, and seven patients receiving 500 mg four times a day for four days gave unacceptable results. The clinical failure rate was five out of 12 and the microbiological failure rate was two out of 12 (six patients failed to return for follow up visits). The clinical responses of patients who were treated for three or four days were, however, better than those of patients given single dose treatment; only one out of four who were evaluable responded clinically.

Of 25 patients in that study who received erythromycin stearate 500 mg three times a day for five days and returned for follow up, 14 had epithelialised lesions and the ulcers of the others had decreased in size. In one case, however, *H ducreyi* was isolated again from the lesion. On day 14 three of the 25 patients defaulted, including the patient with the second positive culture. In the other 22 patients, epithelialisation was either complete (in 20 patients) or almost complete (in one patient). The ulcer in the remaining patient persisted, and *H ducreyi* was isolated again from the lesion. Overall, two treatment failures (8%) were recorded. Thus, although single dose treatment with erythromycin proved to be unsatisfactory, treatment at a dosage of 500 mg three times a day for five days should be adequate.

SULPHONAMIDE AND TRIMETHOPRIM PREPARATIONS

Sulphonamide and trimethoprim combinations have also been widely used to treat chancroid. Sulphamethoxazole and trimethoprim at a dosage of 800 and 160 mg twice a day for 10 days has been advocated as a suitable treatment regimen, and other sulphonamide and trimethoprim combinations have been evaluated in Kenya.^{19,20} Despite encouraging results with sulphamethoxazole and trimethoprim (3200 and 640 mg) as a single oral dose, higher failure rates have been recorded subsequently by the same workers, possibly as a result of the emergence of resistance to trimethoprim. Resistance to trimethoprim has also been recorded in Thailand.¹¹ In southern Africa, isolates remain susceptible to trimethoprim, and sulphamethoxazole and trimethoprim (800 and 160 mg) given twice a day for 10 days continues to be adequate

Table 1 Responses to treatment with four or six capsules of sulphamethopyrazine and trimethoprim (SMP/TMP) of 179 patients with proved chancroid in Carletonville and Harare

	No	No (%) of treatment failures
Carletonville:		
Six capsules	54	4 (7)
Four capsules	48	4 (8)
Harare:		
Six capsules	41	4 (10)
Four capsules	36	2 (6)
Total:		
Six capsules	95	8 (8)
Four capsules	84	6 (7)

treatment (Koornhoof HJ *et al*, unpublished observation). We evaluated two single dose regimens of sulphamethopyrazine and trimethoprim (SMP/TMP) in 77 culture proved cases in Harare, Zimbabwe, and in 102 cases in Carletonville, South Africa. Patients were randomly assigned to treatment with SMP/TMP either six capsules (1200 mg SMP/1500 mg TMP) or four capsules (800 mg SMP/1000 mg TMP) as a single oral dose. Table 1 shows that eight (8%) of 95 patients failed to respond after treatment with six capsules, and six (7%) of 84 patients failed to respond after four capsules. No significant difference in response rates was seen regarding the two dosages or the participating centres. Thus sulphamethopyrazine and trimethoprim or sulphametreole and trimethoprim remain suitable single dose treatments in areas where resistance to trimethoprim has not emerged.

QUINOLONES

H. ducreyi is very susceptible to the new fluoroquinolones.²¹ Treatment with rosoxacin and enoxacin yielded disappointing results in Nairobi,^{22,23} but treatment with ciprofloxacin proved effective.²⁴ In a recent evaluation of 96 patients treated with ciprofloxacin in Johannesburg, 49 received 500 mg and 47 received 1000 mg ciprofloxacin as a single oral dose (unpublished observation). Table 2 shows the response to treatment. Of the 49 patients treated with 500 mg, two failed to respond clinically and yielded *H. ducreyi* again at both follow up visits. In contrast, no clinical treatment failures were recorded in the 47 patients receiving 1000 mg ciprofloxacin. The difference between the two treatment schedules was not, however, significant (Fisher's exact test). A larger series would be required to establish whether this trend was real or apparent.

OTHER ANTIMICROBIAL AGENTS

Several other antimicrobial agents have been evaluated in treating chancroid, most notably in Nairobi, Kenya, and also in Thailand. A most promis-

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Table 2 Clinical response of chancroid in 96 patients treated with ciprofloxacin 500 mg or 1000 mg

Response of genital ulcer to treatment	500 mg (n = 49)	1000 mg (n = 47)
At follow up (seven days):		
Epithelialised	36	34
Not epithelialised	13	14
At follow up (14 days):		
Epithelialised	40	42
Improved but not epithelialised	4	0
Worse	2	0
Did not return	2	5
Lesion open after epithelialising*	1	0

*Patient had not abstained from sexual intercourse.

ing agent was ceftriaxone, which has a conveniently long half life. Given as a single intramuscular injection of 250 mg, cure rates approaching 100% have been achieved (Nsanze H *et al*, unpublished observation).¹¹ Other agents that have yielded appreciable therapeutic benefits include thiamphenicol given as single oral doses of 2.5 g on two successive days²⁵ and spectinomycin 2 g given as a single intramuscular injection.²⁶ Results of a spectinomycin study in Johannesburg, however, showed a less satisfactory response, with seven (13%) of 55 patients failing to respond to a single 2 g injection (Ballard RC *et al*, unpublished observation).

Minocycline was also found to have good activity against *H. ducreyi* (MIC₉₀ 2 mg/l) compared with tetracycline (MIC₉₀ 16 mg/l) and doxycycline (MIC₉₀ 4 mg/l).¹⁴ A comparison of minocycline and doxycycline at Carletonville indicated that minocycline is a candidate for treating chancroid as 29 (91%) of 32 patients responded to the drug 100 mg twice a day for 10 days, but only 20 (59%) of 34 patients treated with doxycycline at the same dosage and for the same duration responded satisfactorily (Ballard RC *et al*, unpublished observation).

RESPONSE OF ULCERS AND LYMPHADENOPATHY TO TREATMENT

Initial responses (usually within 72 hours) to successful treatment of chancroid were a decrease in ulcer pain, the disappearance of the purulent base of ulcers, the onset of epithelialisation, and failure to isolate *H. ducreyi* again. The rate of healing does not appear to depend solely on the antimicrobial agent or the duration of treatment, but was rather a function of the size and site of lesions, especially when they were in a subpreputial location. In contrast to the responses of ulcers, the patterns associated with lymphadenopathy are variable. In a few (about 10%) cases the regional lymph nodes may enlarge and become fluctuant despite the initiation of "successful" treatment. Repeated aspiration of these bubos may be required to prevent inguinal or femoral ulcers. Progression to

fluctuance is associated with a failure to isolate *H ducreyi* from bubos after the start of treatment.

Discussion

The results of these studies indicate that several short course or single dose treatments for chancroid are available for developing societies. Treatment regimens largely depend on the availability of antimicrobial agents, the susceptibility of local isolates to antimicrobials, the relative costs, and the sophistication of diagnostic services. In southern Africa many of the more convenient treatment regimens cannot be employed generally because the antimicrobial agents are not available or cost too much. Diagnostic facilities are also often limited. Furthermore, classic descriptions of genital ulcer disease may be misleading when establishing a diagnosis on clinical grounds alone, and treatment algorithms are therefore required to guide primary health care workers.²⁷ All major causes of genital ulcer disease are encountered in southern Africa, but chancroid and syphilis account for more than 80% of cases.² Benzathine penicillin and one of the regimens described for chancroid could therefore provide a reasonable first line treatment for managing most cases of genital ulcer disease. Similarly, the classic presentation of LGV is that of enlarged painful regional lymph nodes, with or without small primary lesions on the external genitalia. In practice, however, primary lesions of LGV often have a purulent base and may therefore be confused with early chancroid. Conversely, small chancroid lesions may be diagnosed as LGV. As tetracycline (the antibiotic of choice for LGV) is ineffective in treating many cases of chancroid, controversial cases may be treated for 14 days with either erythromycin or minocycline to cater for possible LGV infection. Similarly, confusion between genital herpes and chancroid may cause diagnostic problems when herpetic ulcers are infected secondarily. Treatment with cotrimoxazole or SMP/TMP would prevent progressive ulceration (in cases of chancroid) and would aid healing in cases of herpes with secondary infection.

In conclusion, future prospects for treating laboratory proved cases of chancroid are encouraging, with several short or single dose treatments becoming available. Provision of these treatments will depend on the recognition of chancroid as a public health problem, the susceptibilities of local *H ducreyi* isolates to antimicrobials, the availability of diagnostic facilities, and, inevitably, financial considerations.

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